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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re Application of:

Jacques DUMAS et al.

Examiner: Robinson, Binta M.

Serial No.: 09/640,780

Group Art Unit: 1625

Filed: August 18, 2000

Title: INHIBITION OF RAK KINASE USING SUBSTITUTED HETEROCYCLIC UREAS

APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal filed on June 3, 2003, herewith are three copies of Appellants' Brief on Appeal. The Commissioner is hereby authorized to charge any fees associated with this appeal to Deposit Account No. 13-3402.

This is an appeal from the decision of the Examiner finally rejecting claims 1-4, 9, 11-13, 15, 16, 43, 46, and 78-79 of the above-identified application.

(1) REAL PARTY IN INTEREST

The real party in interest in the present application is Bayer Pharmaceutical Corporation, to whom the present application was assigned in an assignment filed on June 9, 2003, from Bayer Corporation, to whom the present application was assigned on November 9, 2000, from the inventors (date noted is date when the last assignor signed).

(2) RELATED APPEALS AND INTERFERENCES

There are no known related appeals or interferences.

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(3) STATUS OF THE CLAIMS

Claims 1-79 are pending in the present application. Claim 5-8, 10, 14, 17-42, 44, 45, and 47-77 were withdrawn from consideration (withdrawn claims are not subject of this appeal and are thus not reproduced in the Appendix). Claims 1-4, 9, 11-13, 15, 16, 43, 46, and 78-79 were rejected. Claims 1-4, 9, 11-13, 15, 16, 43, 46, and 78-79, i.e., all of the rejected claims, are on appeal. The claims in the appendix include the amendment after final to claim 12 discussed below.

(4) STATUS OF AMENDMENTS AFTER FINAL

An amendment changing the dependency of claim 12 from claim 10 to claim 9 has been filed simultaneously with this Brief on Appeal.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to novel aryl urea compounds of formula I,

$$\text{A-NH-}\overset{\overset{\displaystyle \text{O}}{\|}}{\text{C}}\text{-NH-B} \qquad \text{I}$$

where A and B are defined in the claims and in the specification on page 2, line 22 to page 8, line 21 (not reproduced here),which act as raf kinase inhibitors and are therefore useful as pharmaceuticals for the treatment of a variety of diseases, such as, for example, solid cancers. See specification page 1, lines 1-10, and page 2, lines 1-25. Following a requirement to elect a species, applicants elected isoxazole compounds.

(6) ISSUES

The issue outstanding in this application is whether claims 1-4, 9, 11-13, 15, 16, 43, 46, and 78-79 are enabled under 35 U.S.C. § 112, first paragraph.

The reasons for the rejection are directed to claim 1 in its entirety and not only to the elected subject matter.

(7) GROUPING OF THE CLAIMS

None of the claims stand or fall together.

(8) APPELLANTS' ARGUMENTS

Paper number 17, referred to hereinafter as the Office Action, alleges that the specification does not provide enablement for "A" and "B" equal to all the various groups claimed in the substituted heterocyclic ureas of the claims. Additionally the Office Action and paper number 19, referred to hereinafter as the Advisory Action, both allege that the examples only provide compounds where "B" is phenyl or pyridyl.

Given the specificity of the "A" and "B" groups, especially of the "A" group, it would at most involve routine experimentation if any at all for one of ordinary skill in the art to make and use the claimed invention. The specification provides ample guidance on how these compounds are prepared, i.e., both broad teachings as well as specific reaction schemes to achieve the claimed compound, in addition to pointing to references, i.e., *Comprehensive Heterocyclic Chemistry*; Permagon Press: Oxford, UK (1984), *Advanced Organic Chemistry*, 3rd Ed.; John Wiley: New York, (1985), *Ishizaki et al*, JP 6025221, *Comprehensive Organic Transformations*; VCH Publishers: New York (1989), Rylander. *Hydrogenation Methods*; Academic Press: London, UK (1985), Seyden-Penne. *Reductions by the Alumino- and Borohydrates in Organic Synthesis*; VCH Publishers: New York (1991), which teach their synthesis. See, for example, specification page 18, line 25 to page 23, line 5. Additionally, the specification teaches through examples how to prepare a large number of "A" groups and "B" groups, and also how to form ureas which allow for varying the identity of "A" and "B." See specification page 31, line 15 to end of page 79.

The Office Action nevertheless alleges that applicants only provide examples where "A" is oxazolyl, isoxalolyl, pyrazolyl, thiadiazolyl, and thienyl. Even if this was correct, the examples are more than ample to provide enablement for compounds defined by the full scope of "A," which is a specific and clearly defined group of five-membered heteroaryls comprising pyrazoles, isoxazoles, thiadiazoles, thiophenes, oxadiazoles, oxazoles, tetrazoles, thiazoles and furans. The specification on page 31, line 15 to end of page 39, demonstrates the synthesis of starting materials, wherein A is a pyrazole (bottom of page 32), an isoxazole (tope of page 32), an oxazole (top of page 39), an imidazole (bottom of page 32), a thiophene (bottom of page 34), a thiadiazole (bottom of page 37), an ozadiazole (middle of page 38), a tetrazole (bottom of page 39). Methods for synthesizing furan starting materials and preparing ureas therefrom are known to be consistent with the preparation of the thiopene starting materials and are as illustrated in U.S. Patent Nos. 6,187,799 and 6,344,176. The specification also provides numerous (several hundred) specific compounds

according to the claims. See pages 80-111. Compounds having several of the "A" groups are exemplified. including isoxales, pyrazoles, thiophenes, thiazoles, tetrazole, oxadizol, thiadiazoles. This amount of guidance is more than adequate under the law to enable the preparation of compounds having the claimed "A" groups.

Applicants also disagree with the allegation that the only "B" groups exemplified are phenyl or pyridyl. While most of the exemplified compounds have a "B" group as phenyl or pyridyl, the disclosure is not limited to what is alleged. For example, compound 20 on page 81 has thienyl as "B," and compound 173 on page 93 and compound 246 on page 98 both have indolyl as "B." Furthermore, compound 394 has a fluorene (tricyclic) structure as "B." This compound is not covered by the claims on appeal, but nevertheless, also demonstrates that groups for "B" other than phenyl and pyridyl have been exemplified.

Even absent such disclosure and vast amount of examples, the courts have placed the burden upon the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated; see, e.g., *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971) (holding that how an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance.) The disclosure must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statement contained therein. See *In re Marzocchi*, supra. No such evidence or reason for doubting Applicants' disclosure is provided.

Additionally, "the [enablement] requirement is satisfied if, given what they [, those or ordinary skill in the art,] already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.'" See *Amgen v Hoechst Marion Roussel*, 65 USPQ2d 1385 (CA FC 2003). Making the compounds of the claimed invention having the specific "A" and "B" groups of the claims, would be routine for those of ordinary skill in the art in view of applicant's disclosure. Explicitly providing examples for preparing species having each possible option for each "A" and "B" groups is not necessary to enable the same. See, for example, *Spectra-Physics v Coherent*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987) ("A patent need not teach, and preferably omits, what is well known in the art"); *In re Howarth,* 654 F.2d at 105, 210 USPQ 689 (CCPA 1981) ("An inventor need not ... explain every detail since he is speaking to those skilled in the art."); *In re Gay*, 309 F.2d 769, 774, 135 USPQ 311 (CCPA 1962) ("Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be.")

The specification, even though not necessary for an enabling disclosure, provides numerous, i.e., 397, species of the claimed genus. See specification page 80 to page 111. There is no requirement that an applicant provide examples directed to the preparation of each and every species of a claimed invention. See, for example, *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art"); *Utter v Higara*, 845 F.2d at 998-99, 6 USPQ2d 1714 (CAFC 1988) (holding that a specification may, within the meaning of Section 112, Para. 1, enable a broadly claimed invention without describing all species that claim encompasses). Instead, as discussed earlier, there is no requirement for any examples. See, for example, *Marzocchi*, supra, stating that "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to make the compounds recited in the claims. Instead of relying on proper probative evidence, the rejection is improperly based on the bare allegation that the disclosure does not provide enablement for "A" and "B" equal to all of the claimed rings. No evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the preparation of the claimed compounds without undue experimentation.

There is also adequate disclosure to enable the use of the compounds claimed. The Office Action lists several of the Wands factors and makes allegation with respect to these factors relating to the use of the compounds, but does not provide any factual basis for the allegations regarding these factors.

The only basis given for these rejections are (1) the absence of specific IC_{50} results for each of the exemplified compounds in the cellular assay, and (2) that the applicants allegedly do not provide working examples where "A" is other than oxazolyl, isoxalolyl, pyrazolyl, thiadiazolyl, and thienyl, and where "B" is other than phenyl, pyridyl or thiophenyl rings. See Office Action page 4, lines 4-12. The Office Action elsewhere (see for example page 5, lines 4-6) and the Advisory Action alleges that the only "B" groups exemplified are phenyl and pyridyl.

With respect to allegation (1), applicants point out that each and every one of the 397 compounds tested showed some activity in the *in vitro* raf kinase assay exemplified on pages

111-112. The fact that some variation in activity from species to species is present is immaterial to the enablement issue. The fact that all of the large variety of species tested showed some activity clearly demonstrates that the claimed invention works, i.e., is enabled. The possible variation in activity is not an issue probative for lack of enablement.

There is no need to display the specific results for each compound in the cellular assay. Not having specific results for each tested compound is not a valid basis for an enablement rejection. Applicants provide two types of results, i.e., *in vitro* raf kinase assay results and cellular assay results.

The specification teaches that 96 cell cultures were tested with compound(s) of the invention in a cellular assay. The results are summarized as supporting that "the compounds of Formula I are active to inhibit raf kinase activity and to inhibit oncogenic cell growth." See pages 112-113.

The specification also teaches that each of the exemplified compounds were tested in an *in vitro* raf kinase assay and all the compounds displayed activity, i.e., had an IC_{50} value between 1 nM and 1 μM. See pages 111-112.

The specific results for each compound in the assays are not necessary for enabling the claimed invention. Nevertheless, the Office Action alleges that without the results of cellular assays and in vivo assays undue experimentation would be required to make and use the claimed invention. Applicants provided adequate guidance and examples to the preparation of the claimed compounds, have demonstrated that numerous representative species possess activity, and have provided guidance to those of ordinary skill in the art how to test the claimed compounds (see page 113). Providing more is not necessary to enable the claimed invention.

As discussed above, the law does not require an applicant to test a compound in examples. See, for example, *Marzocchi*, supra, stating that whether "an enabling teaching is set forth, either <u>by use of illustrative examples or by broad terminology, is of no importance</u>." The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, <u>does not turn on whether an example is disclosed</u>." See MPEP § 2164.02.

The disclosure must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statement contained therein. See *In re Marzocchi*, supra. No reasons for such doubt have been provided.

With respect to pharmaceutical inventions, an applicant is not required to test the claimed compounds in their final use. The Federal Circuit in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), stated that

> usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas.

The specification of the application on page 1 teaches that

> It has been shown that inhibiting the effect of active ras by inhibiting the raf kinase signaling pathway by administration of deactivating antibodies to raf kinase or by co-expression of dominant negative raf kinase or dominant negative MEK, the substrate of raf kinase, leads to the reversion of transformed cells to the normal growth phenotype (see: Daum et al. *Trends Biochem. Sci.* 1994, *19*, 474-80; Fridman et al. *J. Biol. Chem.* 1994, *269*, 30105-8. Kolch et al. (*Nature* 1991, *349*, 426-28) have further indicated that inhibition of raf expression by antisense RNA blocks cell proliferation in membrane-associated oncogenes. Similarly, inhibition of raf kinase (by antisense oligodeoxynucleotides) has been correlated in vitro and in vivo with inhibition of the growth of a variety of human tumor types (Monia et al., *Nat. Med.* 1996, *2*, 668-75).

Doubt has been held reasonable where, for example, the invention has been characterized as "highly unusual," *In re Houghton*, 433 F.2d 820 (CCPA 1970), as "incredible," *In re Citron*, 325 F.2d 248, (CCPA 1963), or as "too speculative," *In re Eltgroth*, 419 F.2d 918 (CCPA 1970). Because compounds having similar activities are known in the art, the existence of a new class of compounds having the claimed activities is not objectively doubtable, i.e., not "highly unusual," "incredible," and/or "too speculative."

Thus, the claimed methods of use are proper since the compounds were shown to possess the activity indicative of their usefulness in the claimed methods.

With regard to *Wands*, supra, used by the Examiner as the basis of the rejections, the court therein teaches that whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations. Factors to consider whether a disclosure requires undue experimentation is summarized to include the 8 *Wands* factors (not reproduced here). No factor alone is determinative. The court in *Wands*, further held that the test is not merely quantitative, since

a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Instead of relying on proper probative evidence, the rejection is improperly based on bare allegations and conclusiory statements about the adequacy of the disclosure. No evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the preparation and use of the claimed compounds without undue experimentation.

Applicants provide numerous examples and ample direction in the specification with respect to the direction in which experimentation should proceed, for example:

- provide 397 exemplified species, (see pages 80-111),
- test each of these compounds in an *in vitro* raf kinase assay and demonstrates activity in all the compounds by providing IC_{50} data, (see pages 111-112),
- provides *in vitro* cellular growth assay of tumor cells in 96 cell cultures (the results are summarized as supporting that "the compounds of Formula I are active to inhibit raf kinase activity and to inhibit oncogenic cell growth,") (see pages 112-113),
- teaches the method of testing the inhibitory effect of the compounds on tumors mediated by raf kinase by the claimed compounds in an *in vivo* assay, (see page 113),
- points to prior art method for the *in vivo* testing for the inhibitory effect of the compounds on tumors mediated by raf kinase, (see page 113).

Applicants provide ample evidence to the claimed activity and ample guidance to test the activity of further compounds according to the invention. Any one of the claimed compounds can be tested by routine protocol known to those of ordinary skill in the art. As stated by the court in *Wands*, supra, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Applicants also bring the attention of the Patent Office to applications 09/755,060, and 09/947,761 wherein structurally similar ureas to the claimed ureas are exemplified wherein the group corresponding to "B" of the general formulae of the present claims are naphthyl (see '761 example 17), quinolinyl (see '761 example 18), pyrazolyl (see '060 example 9), thiazolyl (see '060 example 12), and pyrrolyl (see '060 example 18). Attached Appendix B contains the relevant pages of said applications. All of these compounds with various groups for "B" further demonstrate that one of ordinary skill in the art is enabled to

prepare the compounds of the claimed invention.

The current application's specification even goes further than necessary to provide an enabling disclosure by providing guidance to one of ordinary skill in the art as to dosages to be administered. See specification on page 27, lines 20 to 30. A disclosure of dosages, or actually a disclosure of how to obtain dosages, can be evidence that the claims are enabled. In *Cf. United States v. Telectronics, Inc* ., 857 F.2d 778, 785, 8 USPQ2d 1217 (Fed. Cir. 1988) the court found a specification enabling in part because those skilled in the art would know how to conduct a dose response study to determine the appropriate amounts to be used. In the present application applicants do more. They disclose specific doses to be administered.

Applicants submit that the entire scope of claim 1 is enabled and all its dependent claims are enabled for the reasons discussed above.

Claims 78-79

Claims 78 and 79 recite a narrower scope for group "B" than claim 1. Thus, the enablement of the subject matter within these claims is even more clear than that of claim 1.

Claims where "B" is phenyl or pyridinyl

With respect to claims 2, 3, and 4, "B" is phenyl or pyridyl in the compounds defined, which are clearly enabled. The hundreds of specifically exemplified compounds demonstrate a large representative amount of these compounds. Furthermore, no evidence has been provided that one of ordinary skill in the art would not be enabled to prepare compounds having substituted phenyl or pyridinyl groups.

Elected Subject Matter

Applicants also submit that with respect to claims 9, 11-13, 15, 16 and 43, drawn to elected subject matter, i.e., compounds where "A" is isoxazole, the enablement rejection is even less proper. No choice is necessary for group "A."

Claims to Specific Compounds

Claims 11 and 15 are drawn to the use of specifically named compounds. Their preparation is exemplified and the test results indicate that they possess activity. There is absolutely no basis for rejecting these claims for lack of enablement.

In view of the disclosed activities for the claimed compounds and the extensive guidance provided in the specification to make, test and use the compounds of the invention, the reversal of the rejection to the claims is respectfully requested.

Respectfully submitted,

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APPENDIX A

The Claims on Appeal:

1. A method for the treatment of cancerous cell growth mediated by raf kinase comprising administering a compound of formula I

$$\text{A-NH-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-NH-B} \qquad \text{I}$$

wherein B is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl, substituted by one or more substituents independently selected from the group consisting of halogen, up to per-halosubstitution, and X_n, wherein n is 0-3 and each X is independently selected from the group consisting of –CN, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-NR^5C(O)R^{5'}$, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, phenyl, pyridinyl, naphthyl, isoquinolinyl, quinolinyl up to per halo-substituted C_1-C_{10} alkyl, up to per halo-substituted C_2-C_{10} alkenyl, up to per halo-substituted C_1-C_{10} alkoxy, up to per halo-substituted C_3-C_{10} cycloalkyl, and -Y-Ar;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_2-C_{10} alkenyl and up to per-halosubstituted C_3-C_{10} cycloalkyl,

wherein Y is - O-, -S-, $-N(R^5)-$, $-(CH_2)-_m$, -C(O)-, -CH(OH)-, $-(CH_2)_mO-$, $-NR^5C(O)NR^5 NR^{5'}-$, $-NR^5C(O)-$, $-C(O)NR^5-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^5)-$, $-O(CH_2)_m-$, $-CHX^a$, $-CX^a_2-$, $-S-(CH_2)_m-$ and $-N(R^5)(CH_2)_m-$,

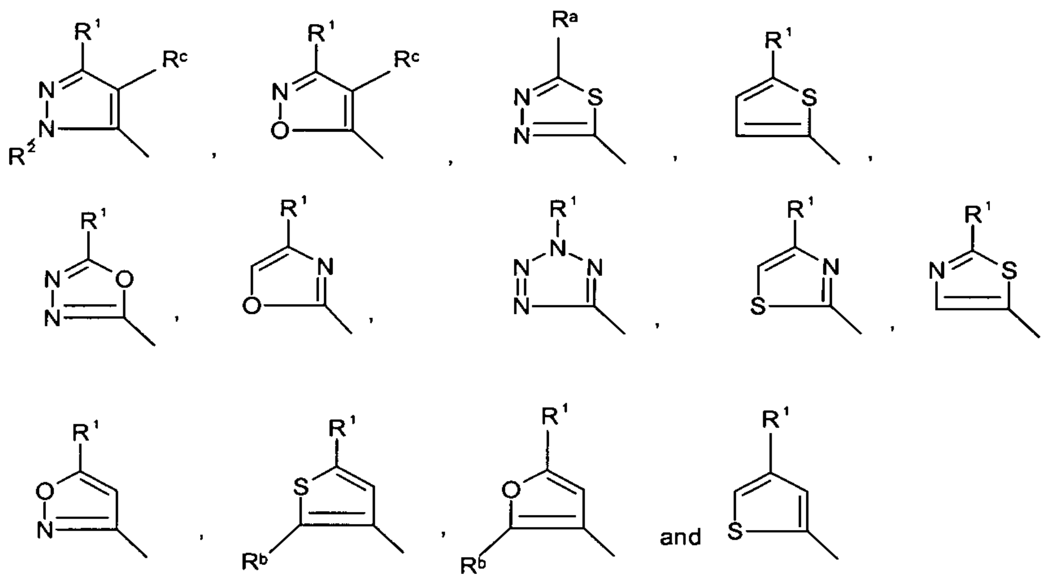
m = 1-3, and X^a is halogen; and

Ar is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl, optionally substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein n1 is 0 to 3 and each Z is independently selected from the group consisting of –CN, =O, $-CO_2R^5$, -$C(O)NR^5R^{5'}$, $-C(O)-NR^5$, $-NO_2$, $-OR^5$, $-SR^5$, $-NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-C(O)R^5$, -

$NR^5C(O)R^{5'}$, $-SO_2R^5$, $SO_2NR^5R^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxyl, C_3-C_{10} cycloalkyl, up to per halo-substituted C_1-C_{10} alkyl, and up to per halo-substituted C_3-C_{10} cycloalkyl,

and

A is a heteroaryl moiety selected from the group consisting of



wherein

R^1 is selected from the group consisting of halogen, C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_1-C_{13} heteroaryl, C_{6-14} aryl, C_{7-24} alkaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{13} heteroaryl, up to per-halosubstituted C_{6-14} aryl, and up to per-halosubstituted C_{7-24} alkaryl;

R^2 is selected from the group consisting of H, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^3R^{3'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, substituted C_1-C_{10} alkyl, substituted C_3-C_{10} cycloalkyl, substituted C_7-C_{24} alkaryl and substituted C_4-C_{23} alkheteroaryl,

where R^2 is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of -CN, - CO_2R^4, $-C(O)-NR^3R^{3'}$, $-NO_2$, $-OR^4$, $-SR^4$, and halogen up to per-halosubstitution,

wherein R^3 and $R^{3'}$ are independently selected from the group consisting of H, $-OR^4$, - SR^4, $-NR^4R^{4'}$, $-C(O)R^4$, $-CO_2R^4$, $-C(O)NR^4R^{4'}$, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, , phenyl, pyridinyl, naphthyl, isoquinolinyl or quinolinyl up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, and up to per-halosubstituted, phenyl, pyridinyl, naphthyl, isoquinolinyl or quinolinyl; and

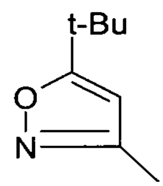
wherein R^4 and $R^{4'}$ are independently selected from the group consisting of H, C_1-C_{10}

alkyl, C_3-C_{10} cycloalkyl, phenyl, pyridinyl, naphthyl, isoquinolinyl, quinolinyl up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_3-C_{10} cycloalkyl, and up to per-halosubstituted, phenyl, pyridinyl, naphthyl, isoquinolinyl or quinolinyl

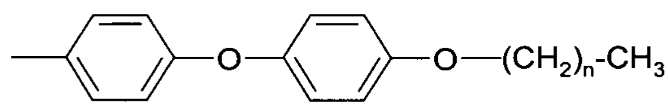
R^a is C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl and up to per-halosubstituted C_3-C_{10} cycloalkyl; and

R^b is hydrogen or halogen,

R^c is hydrogen, halogen, C_1-C_{10} alkyl, up to per-halosubstituted C_1-C_{10} alkyl or combines with R^1 and the ring carbon atoms to which R^1 and R^c are bound to form a 5- or 6-membered cycloalkyl, aryl or hetaryl ring with 0-2 members selected from O, N and S; subject to the proviso that where A is

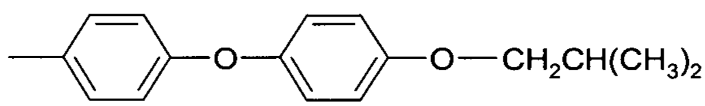


B is not



wherein n = 2-4,

or



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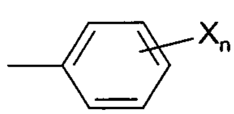
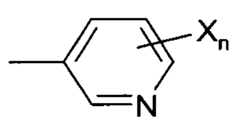
2. A method as in claim 1, wherein B is



or



which is substituted or unsubstituted by halogen, up to per-halosubstitution, and wherein

n = 1-3 and

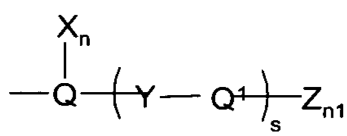
each X is independently selected from the group consisting of C_{1-4} alkyl, up to per-halosubstituted C_{1-4} alkyl and -Y-Ar;

wherein Y is - O-, -S-, $-N(R^5)-$, $-(CH_2)-_m$, -C(O)-, -CH(OH)-, $-(CH_2)_mO-$, $-NR^5C(O)NR^5 NR^{5'}-$, $-NR^5C(O)-$, $-C(O)NR^5-$, $-(CH_2)_mS-$, $-(CH_2)_mN(R^5)-$, $-O(CH_2)_m-$, $-CHX^a$, $-CX^a{}_2-$, $-S-(CH_2)_m-$ and $-N(R^5)(CH_2)_m-$,

m = 1-3, and X^a is halogen; and

Ar is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl, optionally substituted by halogen up to per-halosubstitution and optionally substituted by Z_{n1}, wherein nl is 0 to 3 and each Z is independently selected from the group consisting of –CN, =O, $-CO_2R^5$, $-C(O)NR^5R^{5'}$, $-C(O)R^5$, $-NO_2$, $-OR^5$, $- SR^5$, $- NR^5R^{5'}$, $-NR^5C(O)OR^{5'}$, $-C(O)R^5$, $-NR^5C(O)R^{5'}$, $-SO_2R^5$, $-SO_2R^5R^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl up to per halo-substituted C_1-C_{10} alkyl, and up to per halo-substituted C_3-C_{10} cycloalkyl, wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_2-C_{10} alkenyl and up to per-halosubstituted C_3-C_{10} cycloalkyl

3. A method of claim 1, wherein B is



wherein

Y is selected from the group consisting of –O-, -S-, $-CH_2-$, $-SCH_2-$, $-CH_2S-$, -CH(OH)-, -C(O)-, $-CX^a{}_2$, $-CX^aH-$, $-CH_2O-$ and $-OCH_2-$,

X^a is halogen,

Q is phenyl or pyridinyl,

substituted or unsubstituted by halogen, up to per-halosubstitution;

Q^1 is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl, optionally substituted by halogen up to per-halosubstitution,

X, Z, n and n1 are as defined in claim 1, and s = 0 or 1.

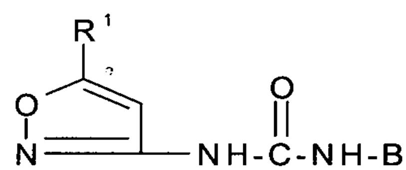
4. A method as in claim 3, wherein

Q is phenyl or pyridinyl, substituted or unsubstituted by halogen, up to per-halosubstitution,

Q^1 is selected from the group consisting of phenyl, pyridinyl, naphthyl, pyrimidinyl, quinoline, isoquinoline, imidazole and benzothiazolyl, substituted or unsubstituted by halogen, up to per-halo substitution, and

each X is independently selected from the group consisting of $-R^6$, $-OR^6$ and $-NHR^7$, wherein R^6 is hydrogen, C_1-C_{10}-alkyl or C_3-C_{10}-cycloalkyl and R^7 is selected from the group consisting of hydrogen, C_3-C_{10}-alkyl, and C_3-C_6-cycloalkyl wherein R^6 and R^7 can be substituted by halogen or up to per-halosubstitution.

9. A method as in claim 1 comprising administering a compound of the formula



wherein R^1 and B are as defined in claim 1.

11. A method as in claim 1 comprising administering a compound selected from the group consisting of:

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-hydroxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(3-hydroxyphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-acetylphenyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-benzoylphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-phenyloxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(3-methylaminocarbonylphenyl)-thiophenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-(1,2-methylenedioxy)phenyl)-oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(3-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pyridyl)thiophenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(3-methyl-4-pyridinyl)oxyphenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(3-methyl-4-pyridinyl)thiophenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(3-methyl-4-pyridinyl)thiophenyl)urea;

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(4-methyl-3-pyridinyl)oxyphenyl)urea;

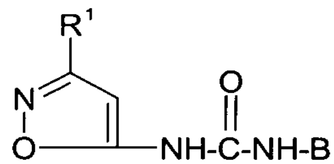
N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(4-(3-methyl-4-pyridinyl)oxyphenyl)urea; and

N-(5-*tert*-Butyl-3-isoxazolyl)-*N'*-(3-(2-benzothiazolyl)oxyphenyl)urea

and pharmaceutically acceptable salts thereof.

12. A method as in claim 9, wherein R^1 is t-butyl.

13. A method as in claim 1 comprising administering a compound of the formula



wherein R^1 and B are as defined in claim 1.

15. A method as in claim 1 comprising administering a compound selected from the group consisting of

N-(3-Isopropyl-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-methoxyphenyl)oxyphenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(5-(2-(4-acetylphenyl)oxy)pyridinyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)methylphenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(4-(4-methyl-3-pyridinyl)oxyphenyl)urea;

N-(3-*tert*-Butyl-5-isoxazolyl)-*N'*-(3-(2-benzothiazolyl)oxyphenyl)urea;

N-(3-(1,1-Dimethylpropyl)-5-isoxazolyl)-*N'*-(4-(4-methylphenyl)oxyphenyl)urea;

N-(3-(1,1-Dimethylpropyl)-5-isoxazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

N-(3-(1,1-Dimethylpropyl)-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(3-(1,1-Dimethylpropyl)-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)thiophenyl)urea;

N-(3-(1,1-Dimethylpropyl-5-isoxazolyl)-*N'*-(5-(2-(4-methoxyphenyl)oxy)pyridinyl)urea;

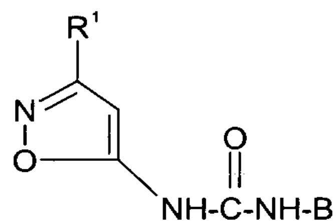
N-(3-(1-Methyl-1-ethylpropyl)-5-isoxazolyl)-*N'*-(4-(4-pyridinyl)oxyphenyl)urea;

N-(3-(1-Methyl-1-ethylpropyl)-5-isoxazolyl)-*N'*-(3-(4-pyridinyl)thiophenyl)urea;

and pharmaceutically acceptable salts thereof.

16. A method as in claim 13, wherein R^1 is t-butyl.

43. A compound of the formula



wherein R^1 is selected from the group consisting of C_3-C_6 alkyl, C_3-C_6 cycloalkyl, up to per-halosubstituted C_3-C_6 alkyl, and up to per-halosubstituted C_3-C_6 cycloalkyl, and

B is phenyl, pyridinyl, indolinyl, isoquinolinyl, quinolinyl or naphthyl, which is substituted by X, optionally substituted by halogen, up to per-halosubstitution, and optionally substituted by X^1_n, wherein n = 0-2;

each X^1 is independently selected from the group of X or from the group consisting of –CN, -CO_2R^5, -$C(O)R^5$, -$C(O)NR^5R^{5'}$, -OR^5, - NO_2, -$NR^5R^{5'}$, C_1-C_{10} alkyl, $C_{2\text{-}10}$-alkenyl, $C_{1\text{-}10}$-alkoxy, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl and C_7-C_{24} alkaryl, and

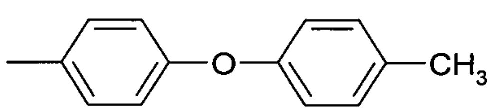
X is selected from the group consisting of -SR^5, -$NR^5C(O)OR^{5'}$, $NR^5C(O)R^{5'}$, C_3-C_{13} heteroaryl, substituted C_1-C_{10} alkyl, substituted $C_{2\text{-}10}$-alkenyl, substituted $C_{1\text{-}10}$-alkoxy, substituted C_3-C_{10} cycloalkyl, substituted C_6-C_{14} aryl, substituted C_3-C_{13} heteroaryl, and –Y-Ar, and wherein if X is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN,
-CO_2R^5, -$C(O)R^5$, -$C(O)NR^5R^{5'}$, -OR^5, -SR^5, -$NR^5R^{5'}$, NO_2, -$NR^5C(O)R^{5'}$,
-$NR^5C(O)OR^{5'}$ and halogen up to per-halosubstitution;

wherein R^5 and $R^{5'}$ are independently selected from H, C_1-C_{10} alkyl, C_{2-10}-alkenyl, C_3-C_{10} cycloalkyl, C_6-C_{14} aryl, C_3-C_{13} heteroaryl, C_7-C_{24} alkaryl, C_4-C_{23} alkheteroaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per-halosubstituted C_{2-10}-alkenyl, and up to per-halosubstituted C_3-C_{10} cycloalkyl, wherein Y is - O-, -S-, -$N(R^5)$-, -(CH_2)-$_m$, -C(O)-, -CH(OH)-, -$(CH_2)_m$O-, -$NR^5C(O)NR^5R^{5'}$-, -$NR^5C(O)$-, -$C(O)NR^5$-, -$(CH_2)_m$S-, -$(CH_2)_mN(R^5)$-, -$O(CH_2)_m$-,
-CHX^a, -$CX^a{}_2$-, -S-$(CH_2)_m$- and -$N(R^5)(CH_2)_m$-,

m = 1-3, and X^a is halogen; and

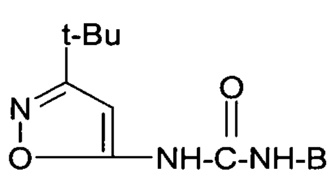
Ar is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl, which is unsubstituted or substituted by halogen up to per-halo and optionally substituted by Z_{n1}, wherein nl is 0 to 3 and each Z is independently selected from the group consisting of –CN, -CO_2R^5, -$C(O)R^5$, =O, -$C(O)NR^5R^{5'}$, -$C(O)R^5$, -NO_2, -OR^5, - SR^5, - $NR^5R^{5'}$, -$NR^5C(O)OR^{5'}$, -$NR^5C(O)R^{5'}$, -SO_2R^5, -SO_2 $R^5R^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, C_3-C_{10} cycloalkyl, substituted C_1-C_{10} alkyl, and substituted C_3-C_{10} cycloalkyl, wherein if Z is a substituted group, it is substituted by one or more substituents independently selected from the group consisting of –CN, -CO_2R^5, -$C(O)NR^5R^{5'}$, =O, -OR^5, -SR^5, -NO_2, -$NR^5R^{5'}$, -$NR^5C(O)R^{5'}$ and -$NR^5C(O)OR^{5'}$, C_1-C_{10} alkyl, C_1-C_{10} alkoxyl, and C_3-C_{10} cycloalkyl,
and where R^1 is –CH_2-t-butyl,

B is not



.

46. A compound of the formula



wherein B is as defined in claim 1.

78. A method as in claim 1, wherein B is phenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, naphthyl, quinolinyl, isoquinolinyl, phthalimidinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, benzofuryl, benzothienyl, indolyl, benzopyrazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl or benzisothiazolyl substituted by -Y-Ar and optionally substituted by halogen up to per-halosubstitution, C_1-C_4 alkyl and up to per-halosubstituted C_1-C_4 alkyl, wherein Y and Ar are as defined in claim 1.

79. A method as in claim 1, wherein B is

a) phenyl, pyridinyl, naphthyl, quinolinyl or isoquinolinyl, substituted by -Y-Ar and optionally substituted by halogen up to per-halosubstitution, C_1-C_4 alkyl and up to per-halosubstituted C_1-C_4 alkyl, wherein Y and Ar are as defined in claim 1;

b) thienyl substituted by methyl; or

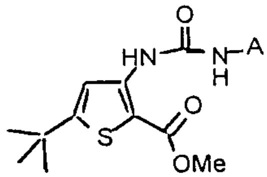
c) indolyl substituted by phenyl or pyridyl.

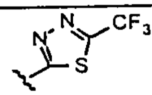
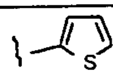
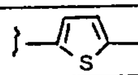
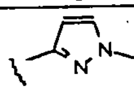
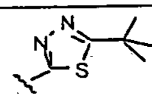
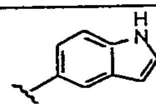
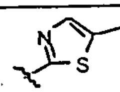
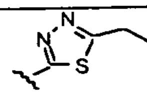
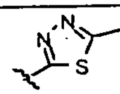
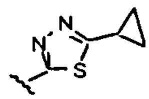
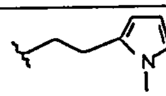
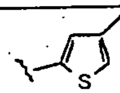
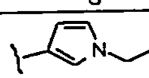
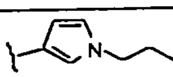
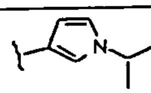
APPENDIX B

Page 15 of application 09/755,060, and pages 65-66 of application 09/947,761 are attached.

09/755,060

Table 2. Heteroaryl substitution for A



Example #	A	Method	mp °C or LRMS
6		E	$(M+H)^+ = 409$
7		F	$(M+H)^+ = 339$
8		F	$(M+H)^+ = 353$
9		E	186-188
10		E	$(M+H)^+ = 397$
11		E	$(M+H)^+ = 372$
12		E	215-216
13		E	168-170
14		E	229-231
15		E	$(M+H)^+ = 381$
16		E	$(M+H)^+ = 364$
17		F	$(M+H)^+ = 353$
18		G	$(M+H)^+ = 350$
19		G	$(M+H)^+ = 364$
20		G	$(M+H)^+ = 364$

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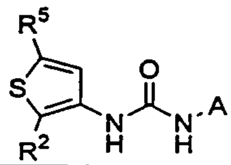
The reaction mixture was separated between with water (10 mL) and EtOAc (10 mL). The aqueous phase was back-extracted with EtOAc (3 x 10 mL), and the combined organic phases were washed with a saturated NaCl solution (25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography (SiO_2; gradient from 20% EtOAc/80% pet. ether to 30% EtOAc/70% pet ether) to give *N*-(3-carbamoyl-5-*tert*-butyl-2-thienyl)-*N'*-(4-methylphenyl)urea (0.092 g, 40 %): ^{1}H-NMR ($CDCl_3$) δ 1.38 (s, 9H), 2.32 (s, 3H), 5.58 (br s, 2H), 6.53 (s, 1H), 7.13 (app d, 2H), 7.35 (app d, 2H), 7.45 (br, 1H), 11.23 (br s, 1H).

The following compounds have been synthesized according to the general methods listed above:

Table 1 3-Urido Thiophenes



#	R^2	R^5	A	mp (°C)	TLC (R_f)	TLC Conditions	MS	MS Source	Method
1	CO_2Me	iPr	C_6H_5	108-10					A
2	CO_2Me	*tert*-Bu	C_6H_5	106-8					A
3	CO_2iPr	*tert*-Bu	C_6H_5	65-7					D
4	CO_2H	*tert*-Bu	4-MeC_6H_4				333 (M+H)	FAB	H
5	CO_2Me	*tert*-Bu	4-MeC_6H_4	124-6					A
6	CO_2Et	*tert*-Bu	4-MeC_6H_4				360 (M^+)	EI	D
53	CO_2Pr-*n*	*tert*-Bu	4-MeC_6H_4	59-66	0.38	10% EtOAc / 90% hex	375 (M+H)	FAB	E
7	CO_2iPr	*tert*-Bu	4-MeC_6H_4	72-86	0.34	10% EtOAc / 90% hex	375 (M+H)	FAB	E
8	CO_2All	*tert*-Bu	4-MeC_6H_4	52-62	0.34	10% EtOAc / 90% hex	373 (M+H)	FAB	E
9	CO_2Me	*tert*-Bu	3-MeC_6H_4	70-2			347 (M+H)	FAB	B

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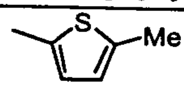
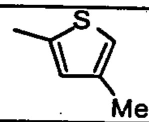
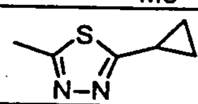
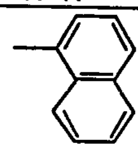
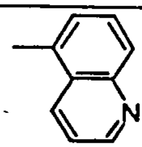
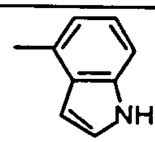
Table 1 3-Urido Thiophenes - continued

#	R^2	R^5	A	mp (°C)	TLC (R_f)	TLC Conditions	MS	MS Source	Method
54	CO_2Me	*tert*-Bu	$4\text{-}FC_6H_4$	160-2	0.45	20% EtOAc / 80% hex	351 (M+H)	FAB	B
10	CO_2Me	*tert*-Bu	$2\text{-}HOC_6H_4$	75-7					B
11	CO_2Me	*tert*-Bu	$2\text{-}H_2NC_6H_4$				348 (M+H)	FAB	C
13	CO_2Me	*tert*-Bu	$3,4\text{-}Me_2C_6H_3$	68-71					A
14	CO_2Me	*tert*-Bu		118-20			353 (M+H)	FAB	J
15	CO_2Me	*tert*-Bu					353 (M+H)	FAB	J
16	CO_2Me	*tert*-Bu		188-9			381 (M+H)	FAB	B
17	CO_2Me	*tert*-Bu		109-11					A
18	CO_2Me	*tert*-Bu		181-2					B
19	CO_2Me	*tert*-Bu		92-3					B
55	CO_2Me	*tert*-Bu	$4\text{-}ClC_6H_4$	150-2					B
56	CO_2Me	*tert*-Bu	$4\text{-}HOC_6H_4$	198-9					B
57	CO_2Me	*tert*-Bu	$4\text{-}H_2NC_6H_4$		0.06	20% EtOAc / 80% hex			C
58	CO_2Me	*tert*-Bu	$4\text{-}EtC_6H_4$				361 (M+H)	FAB	B